Important interactions of immunosuppressants with experimental therapies for novel coronavirus disease (COVID-19)

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Important Interactions of Immunosuppressants With Experimental Therapies for Novel Coronavirus Disease (COVID-19): How to Act

To the Editor:

Transplant recipients are prone to experience severe illness when infected with the new coronavirus disease (COVID-19). Importantly, 2 of the initially proposed drug regimens for the experimental treatment of this disease, lopinavir/ritonavir and chloroquine, could have serious implications on the efficacy and safety of immunosuppressive therapy; moreover, no information is available on the third option, remdesivir. Timely dose adjustment is thus crucial in these patients, and although the drug–drug interactions are known and monitoring of drug levels is warranted, dosing guidance is lacking. Therefore, this letter highlights evidence on the relevant drug–drug interactions and recommends rigorous dose adjustments.

As there are no approved treatment options for severe COVID-19 symptoms, WHO experts recommended promising drugs for trial evaluation, including lopinavir/ritonavir combination, chloroquine, hydroxychloroquine, and remdesivir. Although lopinavir/ritonavir combination showed little benefit in a recent randomized clinical trial,[1] information on their interaction may still be of interest for those who continue using them. Ritonavir is a fast and strong inhibitor of cytochrome P450 isoform 3A (CYP3A). This enzyme limits the uptake of numerous drugs in the intestine and accelerates hepatic drug clearance. The clinical consequence of CYP3A inhibition by ritonavir is a strong increase in the biological availability and half-life of tacrolimus and cyclosporine. A study in healthy subjects showed an extreme 57-fold higher tacrolimus exposure, whereas cyclosporine exposure is less affected with a 6-fold increase.[2] Similar increases in exposure were confirmed in transplant patients with hepatitis C infection and HIV.[3,4] Sirolimus and everolimus concentrations are also expected to increase when used in combination with ritonavir, but no concise data are available. The interaction of sirolimus and everolimus with the strong CYP3A inhibitor ketoconazole led to 10- and 15-fold increases in exposure, respectively.[5,6]

To prevent serious clinical toxicity, dose adjustment for tacrolimus and cyclosporine is essential. When a patient on tacrolimus treatment starts a ritonavir-containing regimen, the tacrolimus dose should immediately be lowered to 0.5 mg once per week or 0.2 mg twice per week.[2] Depending on the time after transplantation, higher maintenance dosages (0.5–1 mg per 48 hours) may apply.[7] In case of ritonavir initiation during stable cyclosporine treatment, reduction to one-fifth of the total daily dose is recommended and should be administered once per day.[2] Although sirolimus dosage reductions to 1.5 mg per week and 1 mg per 14 days have been advised,[8] no case reports are available for everolimus. It is advised to frequently monitor immunosuppressant drug levels, at least right before dose administration. As the drugs' half-lives are expected to increase, it could take several weeks until trough levels are stable (40 and 15 days for tacrolimus and cyclosporine, respectively).[2]

Consequently, ritonavir discontinuation requires an increase in the immunosuppressant dosage. As ritonavir irreversibly inhibits CYP3A, their interaction is assumed to slowly dissipate owing to the turnover of intestinal and hepatic CYP3A enzymes.[9] Calcineurin or mechanistic target of rapamycin (mTOR) inhibitor dosage may be gradually increased by 20% of the original dose each day after ritonavir cessation, and therefore, the original dose could be reintroduced on the fifth day. Frequent monitoring of trough levels is recommended to ascertain optimal treatment.

The antimalarial drugs, chloroquine and hydroxychloroquine, are other treatment options. The product information of chloroquine mentions that chloroquine increases the risk for QTc prolongation and that combination with cyclosporine potentially increases cyclosporine levels, as 2 dated case reports indicated a 3- to 4-fold increase in cyclosporine exposure.[10] There are no publications available on the drug–drug interaction of chloroquine with tacrolimus, sirolimus, or everolimus. As previously mentioned, CYP3A inhibition caused a 10-fold greater increase in tacrolimus exposure compared with cyclosporine exposure. Thus, tacrolimus exposure might be affected by chloroquine in the same manner. Therefore, we advise to be vigilant of this possible interaction and to monitor calcineurin and mTOR inhibitor trough levels at both the start and discontinuation of chloroquine treatment.

There is no information on the possible effects of remdesivir, the third treatment option, on CYP3A. Frequent monitoring is needed when this drug is administered concomitantly with an

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immunosuppressant, and we urge to publish any experience with this combination.

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Measurement Uncertainty in Forensic Toxicology

To the Editor:

Forensic toxicology is a complex discipline in which the detection and accurate measurement of substances can have significant ramifications in legal cases, recruitment, and employment. Analytical measurements must be precise, accurate, and correctly reported, and if high standards are not maintained, there is a strong likelihood that tragic errors will occur. Unfortunately, there is an intrinsic uncertainty associated with making measurements, which can variously be attributed to the operator, instrumentation, analytical method, or specimen integrity. Although analytical bias can, to a certain extent, be evaluated and corrected through the appropriate validation of analytical methods and effective quality control procedures in routine practice, random error cannot be completely addressed, and it is inevitable that *slightly* different results will be obtained for a specimen analyzed several times using the same method. In analytical toxicology, measurement uncertainty can be quantified, thereby providing a clear indication of the variability of a measurand in repeated measures of the same substance using the same method, controls, and instruments. Uncertainty is thus expressed in the form of a dispersion value, such as a SD or a confidence interval, and allows toxicologists to interpret results more critically.

Although the International Organization for Standardization (ISO) requires the measurement of uncertainty, the methods used to calculate this uncertainty is not imposed (ISO 15189/17025). Accordingly, the choice of the calculation method is at the discretion of the testing laboratories. Moreover, diverse guidelines and methodologies have been proposed for the calculation of uncertainty.[1–3]

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Using Nordtest's approach,[1] uncertainty can be calculated based on within-laboratory and between-laboratory reproducibility through independent tests of internal and external quality controls. Nordtest's flow scheme comprises the following 6 defined steps: (1) definition of the quantity to be measured (measurand); (2) determination of within-laboratory reproducibility components (R_w); (3) calculation of bias components using certified reference materials and between-laboratory comparison, that is, the root mean square of the bias values (RMS_{bias}) and the uncertainty of certified or nominal values [u(Cref)]; (4) conversion of components to standard uncertainty, that is, the uncertainty component for within-laboratory reproducibility [$u(R_w)$] and the uncertainty component for the method and laboratory bias [u(bias)], where $u(bias) = \sqrt{RMS_{bias}^2 + u(Cref)^2}$, $RMS_{bias} = \sqrt{\frac{\sum bias_i^2}{n}}$, and u(bias) is the uncertainty of bias; (5) calculation of combined standard uncertainty (u_c), where $u_c = \sqrt{u(R_w)^2 + (u(bias))^2}$; and (6) calculation of the expanded uncertainty (U), where $U = 2 \times u_c$, to reach an approximate confidence interval of 95%. However, although this approach is the simplest means of evaluating measurement uncertainty in forensic toxicology because calculation procedures are simple and external quality controls may be provided by scientific associations, it only produces an overall uncertainty value and lacks information on the individual contribution of each source of uncertainty.

The "Guide to the Expression of Uncertainty in Measurement" (GUM) provides well-established alternative guidelines for evaluating and reporting measurement uncertainty and for a number of years has been considered a standard reference.[2] Although the GUM approach is not formally imposed, the ISO does recommend it and has provided additional guidelines in a recent technical note (ISO/TS 20914:2019).[4] The GUM method for uncertainty calculation can be itemized as follows: (1) definition of the measurand, (2) identification of parameters likely to produce significant uncertainty, (3) estimation of the